Our Case No. 10709/35

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ungashe et al.

Serial No. 10/716,183

Filing Date: November 18, 2003

For: Bis-Aryl Sulfonamides

Examiner Peter G. O'Sullivan

Group Art Unit No. 1621

DECLARATION OF ANDREW M. K. PENNELL
UNDER 37 C.F.R § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Andrew M. K. Pennell, declare the following:

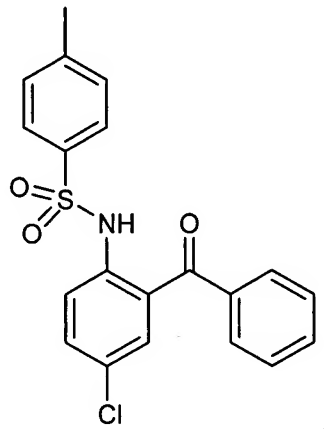
1. I am one of the inventors of U.S. patent application 10/716,183 (the '183 application).
2. I am a citizen of United Kingdom and a resident of 442 Arlington Street, San Francisco, CA 94131, USA.
3. I am a Director in Medicinal Chemistry Department at ChemoCentryx, Inc. My formal education occurred at the Imperial College, London University (B.Sc., Chemistry and Ph.D., Chemistry). I did post-doctoral training at Columbia University, New York.
4. I have been a practitioner of medicinal chemistry for the past 12 years, including positions as Director of Medicinal Chemistry at Genesoft and Chemistry Project and Team Leader in Medicinal Chemistry at Glaxo-Wellcome before joining the ChemoCentryx, Inc. I have authored or co-authored 10 publications in peer-

reviewed journals. I have extensive experience in the patent field named as an inventor on more than two dozen pending or issued US patents and applications and foreign equivalents.

5. I am familiar with the '183 application and its filewrapper, including the Office Action dated August 29, 2005.

6. The above application is directed at modulators of CCR9.

7. The Office Action dated August 29, 2005 rejects the claims as anticipated or alternatively obvious over Wu (Chem. Abst. 123:285437) and Schewe (DE 3544409). The cited references both disclose N-(2-benzoyl-4-chlorophenyl)-4-methyl-benzenesulfonamide:



8. This compound differs from the claims in the '183 application because it has a methyl substituent in the ring attached to the sulfonyl group. In the '183 application, substituents, X, in the ring attached to the sulfonyl group include unsubstituted C_{2-8} alkyl and substituted C_{1-8} alkyl, but not methyl.

9. The compounds of Wu are inhibitors of rice growth. Those of Schewe are inhibitors of lipoxygenase and cyclooxygenase. Neither disclose CCR9 activity.

10. The compounds of the present application are CCR9 modulators.

11. As described at pages 57-60, paragraphs [00179]-[00188] of the '183 application, the efficacy of CCR9 modulators can be measured using a variety of assays including calcium signaling assays and chemotaxis assays.

12. Calcium signalling assays are described at page 59, paragraph [00187] of the '183 application. Generally, calcium signaling assays are used to determine the ability of a modulator to interfere with binding between CCR9 and a known CCR9

ligand, by measuring an intracellular response, calcium flux. CCR9-expressing cells (such as a T cell line MOLT-4 cells) are first incubated with a compound of interest, such as a potential CCR9 antagonist, at increasing concentrations. The cell number can be from 10^5 to 5 x 10^5 cells per well in a 96-well microtiter plate. The concentration of the compound being tested may range from 0 to 100 μM. After a period of incubation (which can range from 5 to 60 minutes), the treated cells are placed in a Fluorometric Imaging Plate Reader (FLIPR®) (available from Molecular Devices Corp., Sunnyvale, CA) according to the manufacturer's instruction. The FLIPR system is well known to those skilled in the art as a standard method of performing assays. The cells are then stimulated with an appropriate amount of the CCR9 ligand TECK (e.g. 5-100 μM final concentration) and the signal of intracellular calcium increase (also called calcium flux) is recorded. The efficacy of a compound as an inhibitor of binding between CCR9 and the ligand can be calculated as an IC_{50} (the concentration needed to cause 50% inhibition in signaling).

13. Chemotaxis assays are described at page 60, paragraph [00188]. In brief, chemotaxis assays used to assess the ability of a modulator to interfere with receptor function by measuring a relevant biological function, migration of cells. CCR9-expressing cells (such as MOLT-4) are first incubated with a compound of interest, such as a possible CCR9 antagonist, at increasing concentrations. Typically, fifty thousand cells per well in a 96-well microchamber (called ChemoTX™) are used but the amount can range from 10^3-10^6 cells per well. The ChemoTX system is well known to those skilled in the art as a type of chemotactic/cell migration instrument. CCR9 ligand TECK, typically at 50 nM (but can range from 5-100 nM), is placed at the lower chamber and the migration apparatus is assembled. Twenty microliters of test compound-treated cells are then placed onto the membrane. Migration is allowed to take place at 37 °C for a period of time, typically 2.5 hours. At the end of the incubation, the number of cells that migrated across the membrane into the lower chamber is then quantified. The efficacy of a compound as an inhibitor of CCR9-mediated cell

migration is calculated as an IC_{50} (the concentration needed to cause 50% inhibition in signaling). Efficacious compounds have low IC_{50} values.

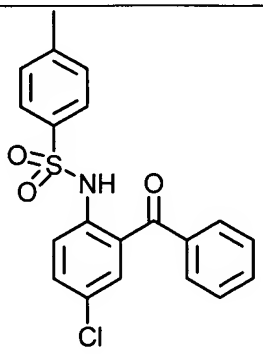
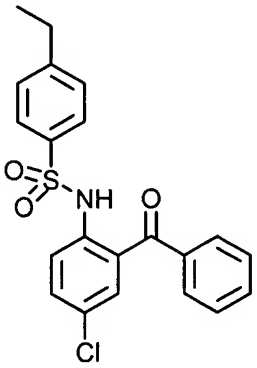
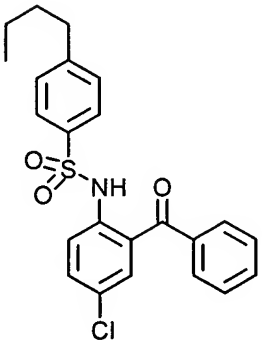
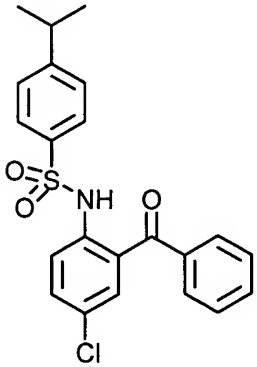
14. The therapeutic potential of CCR9 modulators is thought to involve the inhibition of T-cell migration.

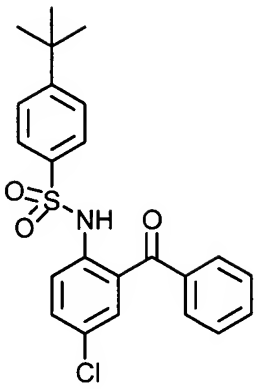
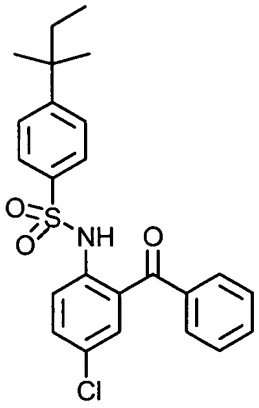
15. Calcium signalling assays were traditionally used in the art to screen for modulators of chemokine receptors. However, it is now well accepted that chemotaxis assays are better screens, because they primarily measure of the antagonism of the relevant biological response, cell migration.

16. Our company screens with both assays, but I predominantly rely on the chemotaxis assay to assess potential drug candidates. I have provided the results of both assays in accordance with the duty of disclosure.

17. The results reported in Table 1 were obtained using the above described assays. A comparison of the the chemotaxis cell migration and calcium mobilization assay data of N-(2-benzoyl-4-chlorophenyl)-4-methyl-benzenesulfonamide (comparative example 1) and compounds of the present invention (entries 1-5) are reported in Table 1:

Table 1: Chemotaxis and Calcium Mobilization Assay Data

Entry	Structure	Chemotaxis IC_{50} (migration, nM)	Calcium Mobilization IC_{50} (FLIPR, nM)
Comparative Example 1		6828	259
1		547	302
2		3756	700
3		520	1390

4		196	3461
5		82	7683

18. As can be seen in Table 1, N-(2-benzoyl-4-chlorophenyl)-4-methyl-benzenesulfonamide (comparative example 1) is a poor CCR9 modulator, compared to compounds of the current invention 1-5, which display chemotaxis potency increases of between 2 fold and 80 fold relative to this comparative example 1.

19. It is declared by the undersigned that all statements made herein of undersigned's own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U. S. C. 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

November 17, 2005

Andrew M. K. Pennell